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Special considerations for vitamin D in the South Asian population in the UK

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ABSTRACT:

The human requirement for vitamin D is achieved primarily through the synthesis of this pre-hormone in the skin during exposure to UVB radiation, with only a minor contribution from the diet year-round. Achieving optimal vitamin D status is therefore largely dependent upon adequate exposure of the skin to sunlight, however the length of exposure required varies with latitude and season, and is also dependent upon skin pigmentation with darker skin requiring greater exposure than fair skin due to the protective effects of melanin against ultraviolet B (UVB) radiation. In northern European latitudes, where UVB radiation between the months of October and March is of insufficient intensity for the synthesis of vitamin D via this route, vitamin D deficiency is a public health concern, particularly for South Asian diaspora and other dark skinned ethnic minority communities. The consequences of vitamin D deficiency include poor bone health, including rickets and osteomalacia. In addition there is increasing awareness of an important role for vitamin D in the development and progression of chronic diseases including type 2 diabetes which is prevalent in South Asian populations. The aim of this review is to examine some of the most recent reports of vitamin D status in South Asian diaspora communities, and to explore its impact on bone health. In addition, we will examine the putative association between type 2 diabetes and vitamin D deficiency in South Asian populations and the current guidelines for treatment of vitamin D deficiency of South Asians in primary care settings. .

KEYWORDS: South Asian, vitamin D, bone health, insulin resistance, diabetes

Introduction

Vitamin D can be obtained from diet (oily fish and liver oils), however the human requirement for vitamin D is achieved primarily through the synthesis of this pre-hormone in the skin during exposure to ultraviolet B (UVB) radiation, with only a minor contribution from the diet year-round [Ashwell *et al.*, 2010, Darling *et al.*, 2013]. Vitamin D status is assessed by measuring 25 hydroxy vitamin D (25(OH)D) levels circulating in the blood plasma or serum. Although there has been much debate over the definition of adequate and optimal vitamin D status based on blood 25(OH)D levels, there is general consensus that values <25 nmol/L (10ng/ml) indicate deficiency and ≥50 nmol/L (20ng/ml) indicate sufficiency. The variations to this proposed by different international expert panels are effectively summarised by Spiro and Buttriss (2014) [Spiro *et al.*, 2014].

The potential consequences of vitamin D deficiency are wide-ranging. Vitamin D receptors are present in many cell types and almost every human tissue, and vitamin D is an important regulator of the expression of genes regulating key metabolic processes. It is not surprising therefore, that deficiency has been linked to increased prevalence of a broad range of medical conditions, including muscular skeletal disorders, cardiovascular disease, cancer, autoimmune disorders and type 2 diabetes [Holick, 2007].

Achieving optimal vitamin D status is largely dependent upon adequate exposure of the skin to sunlight, however the length of exposure required varies with latitude and season. It is also dependent upon skin pigmentation with darker skin requiring greater exposure than fair skin because melanin absorbs UVB radiation in the 290-320nm range and functions as a light filter determining the amount of incident UV radiation available for the cutaneous production of previtamin D3 [Norman, 1998]. In northern European latitudes, UVB radiation between the months of October and March is of insufficient intensity for the synthesis of vitamin D via this route, thus deficiency is of public health concern, particularly for South Asian (SA) diaspora (defined as people originating from India, Pakistan, Sri-Lanka, Bangladesh) and other darker skinned ethnic minority communities in the UK [Mavroeidi *et al.*, 2010, Patel *et al.*, 2013].

Risk factors for SA communities in the UK.

Vitamin D deficiency is estimated to affect the majority of the UK SA population, with one report suggesting that this may be as high as 94% of the SA population in the winter, and 82

% in the summer [Pal *et al.*, 2003]. This high prevalence can be accounted for by several risk factors that are particular to the SA population, including poor dietary intake of vitamin D as many SAs in the UK follow religions with an emphasis on a vegetarian diet, which is low in vitamin D content [Dobbs J, 2006]. However some Bangladeshi populations may have a lower prevalence of deficiency due to a diet that includes the regular consumption of oily fish. The protective effect of melanin in SA skin that limits cutaneous vitamin D synthesis is compounded by the cultural needs to cover the body amongst many SA women. Studies conducted around the world report lower vitamin D status in veiled women compared to males or females adopting Western dress [Alshishtawy, 2012], however sun avoidance when outside is common to both male and female SA adults. Kift et al [Kift *et al.*, 2013] conducted a prospective cohort study comparing the seasonal variation in vitamin D status in SA and white adults living in Manchester, UK over a 12 month period. The study revealed a marked seasonal variation in both groups. In summer, the median 25(OH)D level in the SA group was 9.0 ng/ml, falling to 5.8 ng/ml in winter [Kift *et al.*, 2013]. This compared with values in the white population of 26.2 ng/ml in summer and 18.9 ng/ml in winter. The majority of SAs never reached sufficiency in vitamin D status at any point during the year. Ultraviolet (UV) dosimeters used to record personal UV exposure revealed lower UV exposure among SAs, despite spending similar amounts of time outdoors. Sun exposure diaries completed by the participants also reported lower amounts of skin surface exposure in the SA group suggesting sun avoidance when outside [Kift *et al.*, 2013]. Other studies using simulated courses of summer sunlight in SA adults in controlled dosimetric conditions have confirmed the efficacy of sunlight exposure doses equivalent to 45 minutes of unshaded noontime summer sunlight at 53.5°N (Manchester, United Kingdom) in raising vitamin D status [Farrar *et al.*, 2011, Farrar *et al.*, 2013]. While it has been reported that a higher dose of UV radiation is required to increase plasma 25(OH)D concentration in SAs than Caucasians, the capacity to produce vitamin D is no different between the two ethnic groups [Lo *et al.*, 1986].

Bone Health

Despite the well- established mechanistic link between vitamin D, parathyroid hormone (PTH) and calcium homeostasis described in other papers within this special edition of *Therapeutic Advances in Musculoskeletal Diseases*, evidence for an impact of poor vitamin D status on bone health in UK SA populations is conflicting.

Observational studies exploring the relationship between vitamin D status, bone quality and biochemical markers of bone turnover have been undertaken. Lowe et al [Lowe *et al.*, 2010], studied the vitamin D status and markers of bone turnover in postmenopausal Caucasian and SA women living in the UK. Bone quality was assessed using broadband ultrasound attenuation. Although the SA women had significantly higher serum PTH and lower 25(OH)D concentrations than Caucasian women, this was not associated with significantly higher markers of bone resorption, or reduced bone quality in the SA women. Similar results were reported by Patel et al [Patel *et al.*, 2013] who undertook a large cross sectional study examining vitamin D status and numerous health outcomes including osteoporosis in UK minority ethnic groups. The study included over one thousand SA adults, aged > 45 years recruited from 20 primary care practices in Birmingham, UK. Severe vitamin D deficiency (25(OH)D < 6ug/l) was reported in 42% of the SA participants, however poor vitamin D status was not found to be associated with elevated incidence of osteoporosis, measured using Dual X-ray Absorptiometry (DXA), in this ethnic group [Patel *et al.*, 2013]. In contrast, in a study of young SA women living in the UK (mean age 29 years) [Roy *et al.*, 2007] , DXA revealed that a decrease in serum 25(OH)D of ≤ 15ng/ml was associated with a reduction in bone mass at the hip and wrist.

Intervention studies have also been undertaken to examine the effect of vitamin D supplementation of deficient women on bone health. In a randomised control trial conducted in postmenopausal SA women, Von Hurst [Von Hurst *et al.*, 2010] reported that vitamin D supplementation (4000 IU (100 μg) vitamin D3 daily) significantly increased serum 25(OH)D from Median (25th, 75th percentiles) 21 (11, 40) to 75 (55, 84) nmol/l, and this was associated with significantly lower markers of bone resorption compared to the placebo control group. They concluded that correcting vitamin D deficiency in older women suppresses the age-induced increase in bone turnover and reduces bone resorption which would normally be exacerbated in conditions of low serum 25(OH)D [Von Hurst *et al.*, 2010]. A recent study examining tibial tenderness as a diagnostic measure of vitamin D status also reported a positive improvement in tenderness score following high dose vitamin D supplementation (1.8 million IU (45 mg) of vitamin D3 in split doses), in Pakistani women at high risk for deficiency [Ali *et al.*, 2013].

As mentioned previously, 25(OH)D status exhibits marked seasonal variation, however this variation in muted in SA women, due to reduced sunlight exposure during the summer months. Darling et al [Darling *et al.*, 2014] hypothesised that a high degree of seasonal cycling of 25(OH)D increased bone resorption, and conducted a longitudinal study of SA and Caucasian women in which 25(OH)D was measured once per season, along with PTH and C-terminal telopetide of type 1 collagen (CTX) which is released during the resorption of mature bone. The study confirmed this hypothesis, revealing that the amplitude of the seasonal change in 25(OH)D was positively associated with elevated PTH and CTX [Darling *et al.*, 2014]. This finding also concurs with the hypothesis put forward by Vieth that large seasonal fluctuations in 25(OH)D are associated with adverse health outcomes [Vieth, 2004].

Type 2 diabetes mellitus

Vitamin D deficiency is prevalent in diabetic patients, and could be as high as in 91% patients with diabetes [Alam *et al.*, 2012]. While this observation is not evidence for a causal link, vitamin D specific receptors have been identified in β-pancreatic cells [Mathieu *et al.*, 2005] and there is some evidence suggesting a crucial role for vitamin D status in the pathogenesis of type 2 diabetes mellitus (T2DM), via direct and indirect mechanisms that impact on β-cell function [Pittas *et al.*, 2007] . However the evidence from human studies remains conflicting.

A systematic review undertaken by Mitri et al in 2011 [Mitri *et al.*, 2011] examined both longitudinal observations studies of vitamin D status and randomized controlled trials (RCTs) of vitamin D supplementation on glycemic outcomes. Meta-analysis of the longitudinal data from three observational cohort studies revealed that there was a statistically significant overall reduction in relative risk of the development of newly diagnosed T2DM in those who consumed >12.6 μg/day compared with those who consumed <5/ μg/day. Combining data from 5 cohort studies that measured baseline blood 25(OH)D concentration revealed that there was a significant inverse relationship between blood 25(OH)D and risk of developing T2DM, with individuals with a 25(OH)D >25ng/ml having a 43% lower risk than those with 25(OH)D <14 ng/ml [Mitri *et al.*, 2011]. This observation was confirmed in a recent prospective observational study of prediabetic patients in the USA, after adjusting for other lifestyle factors [Pittas *et al.*, 2012]. Mitri [Mitri *et al.*, 2011] undertook summary of the data from 3 RCTs identified by the systematic search that examined the impact of infrequent, high

dose vitamin D supplementation (100,000 IU given once; 40,000 IU/week for 26 weeks; 100,000 or 200,000 IU given once) in patients with established T2DM. The analysis revealed no improvement in the glycaemic indicators in these patients. In addition, summarising data from 4 RCTs that examined the impact of vitamin D supplementation (doses ranging from 5714 to 8571 IU/day) on insulin resistance in participants with normal glucose tolerance revealed no significant effect, with the exception of one trial [Von Hurst *et al.*, 2010] that reported an improvement in insulin resistance following vitamin D supplementation (4000 IU/day) in non-diabetic, SA women with insulin resistance at baseline. Taken together, this indicates that there is an inverse relationship between vitamin D status and risk of developing T2DM, however "normalising" vitamin D status through supplementation in patients with established T2DM does not improve glycaemic outcomes, however there may be some genetically determined differences in this glycaemic response to supplementation that also involves parathyroid hormone (PTH) and Ca metabolism [Jain *et al.*, 2012].

Studies in SA populations with T2DM.

South Asian communities have a 4-6 fold greater rate of persons with T2DM than white British communities, [Barnett *et al.*, 2006] and there have been a number of recent studies investigating the relationship with vitamin D status and T2DM in this ethnic group. A small cross sectional study conducted in SA in the UK revealed a significantly higher prevalence of hypovitaminosis (defined as a 25-hydroxyvitamin D < 50 nmol/l) in with T2DM (83%) compared to the non- diabetic control group (70%), although there was no difference in the prevalence of vitamin D deficiency (defined as 25-hydroxyvitamin D <12.5 nmol/l) between the two groups (13% vs 19% respectively) [Tahrani *et al.*, 2010]. In addition, there were no overall significant differences in the mean HbA1c levels between patients with and without vitamin D deficiency, however vitamin D deficient women did have higher glycated haemoglobin (HbA1c) levels than the rest of the diabetic cohort. Linear regression analysis revealed that vitamin D deficiency was independently related to HbA1c in women with T2DM, but not in men [Tahrani *et al.*, 2010].

Metabolic syndrome, (a condition that includes insulin resistance, visceral adiposity, atherogenic dyslipidemia and endothelial dysfunction [Huang, 2009]) is also prevalent in SA populations. George et al [George *et al.*, 2013] examined the association between 25(OH)D

and PTH with metabolic syndrome in SA (Indian) adults living in South Africa to determine whether ethnic differences in 25(OH)D levels or PTH levels contribute to difference in the prevalence of metabolic syndrome. The study revealed that SAs had significantly higher fasting glucose, lower 25(OH)D levels and were more insulin resistant than non SAs. The prevalence of vitamin D deficiency (<30 nmol/l) was 3% in African and 15% in SA. The prevalence of metabolic syndrome was higher in the SA's (46%), compared to Africans (19%), however no statistically significant association between vitamin D status, and metabolic syndrome or its components was identified [George *et al.*, 2013]. Similarly, a study in Oslo Norway was undertaken to examine the reason for the greater prevalence of insulin resistance and T2DM in people of SA ethnicity [Wium *et al.*, 2013]. Vitamin D deficient patients (25(OH)D≤ 50 nmol/l) with T2DM were recruited, 43 of northern European origin and 19 SA. There was evidence of ethnic differences in fasting endogenous glucose production, with higher levels found in SA, however there was no significant correlation between 25(OH)D and insulin sensitivity or insulin secretion in either ethnic group or in the cohort as a whole [Wium *et al.*, 2013].

Gestational diabetes is also more prevalent in SA women than in Caucasian women [Gunton *et al.*, 2001]. Whitelaw et al [Whitelaw *et al.*, 2014] undertook a cross sectional study in UK pregnant women undergoing glucose tolerance testing at 26 weeks gestation to explore potential links between lower vitamin D status, ethnicity and glucose metabolism during pregnancy. Of the 1467 women included in the study, 53.4% of the women were of SA origin, with 40.6% describing themselves as European (including British). The selection criteria excluded women with pre-gestational diabetes. Vitamin D status, PTH levels, plasma glucose and serum insulin and calcium were included in the biochemical analyses. Vitamin D status was significantly higher in the European compared to the SA women, with 93% of SA and 66% of European women deficient (25(OH)D<20 ng/ml) [Whitelaw *et al.*, 2014]. Fasting and post challenge glucose and fasting insulin concentrations were lower among European women than SA women, however there were no statistically significant associations between, vitamin D status and glucose tolerance in pregnancy, and it was concluded that lower 25(OH)D does not explain ethnic differences in the risk of gestational diabetes. However, some interesting associations between serum calcium and fasting insulin and the risk of developing

gestational diabetes were noted, irrespective of ethnicity in this cohort [Whitelaw *et al.*, 2014].

Combinations of calcium and vitamin D have also been studied. One of the largest observational studies was the Women's Health Initiative study of 33,951 receiving calcium (1000 mg) plus vitamin D (400 IU) supplements daily, revealed there was no reduction in the risk of developing diabetes over 7 years [De Boer *et al.*, 2008]. It is not stated in this study how many of the participants were South Asian, however 2% were stated as being of Asian/Pacific Island which would include the South Asian sub group). Interestingly, a study conducted in the UK [Sabherwal *et al.*, 2010] investigated the effect of vitamin D and calcium supplementation on glycemic control in SA patients with established T2DM and vitamin D inadequacy. A total of 52 patients diagnosed with T2DM for more than 3 years were included in this study. A baseline, 29 were vitamin D deficient (<25 nmol/l) and 23 insufficient (≤50 nmol/l). Supplementation with 10 µg/day (400 IU) vitamin D and 1200 mg Ca/day resulted an increase in serum 25(OH)D to normal levels, and a decrease in glycated haemoglobin, HbA1c. There was a significant negative correlation between change in Hb1Ac and change in vitamin D levels post treatment (r-0.305) suggesting that vitamin D replacement therapy combined with Ca may be beneficial for glycaemic control in SA patients [Sabherwal *et al.*, 2010].

Management of vitamin D deficiency in South Asians within the primary care setting

In 2012, the Chief Medical Officers for the United Kingdom sent out a letter to General Practitioners, Practice Nurses Health Visitors and Community Pharmacists to raise the awareness of vitamin D deficiency particularly amongst the high risk groups in the UK population, which includes people who have darker skin of SA origin [Chief Medical Officers for the United Kingdom, 2012] . They recommended that these group of patients should take a daily supplement containing 10µg (400 IU) of vitamin D. This has recently been confirmed by the Scientific Advisory Committee on Nutrition (SACN) in the most recent (2016) report on vitamin D and health [Sacn, 2016] in which a reference nutrient intakes (RNI) of 10 µg per day is now recommended for all over the age of 4 years, including "population groups at increased risk of vitamin D deficiency". Recognising that this is difficult to achieve from natural dietary sources unless oily fish is consumed daily, Public Health England also suggests that people

from at risk groups, including darker skinned ethnic minorities, should consider taking a daily supplement of 10 µg throughout the year.

In 2014 the National Institute for Health and Care Excellence (NICE) released guidelines entitled “Vitamin D: increasing supplement use in at-risk groups” [National Institute for Health and Care Excellence, 2014]. The “at risk” group included those who have low or no exposure to the sun including those who cover their skin for cultural reasons and people with darker skin, including SAs. The emphasis in this guideline is around a multi agency approach in raising the awareness of vitamin D deficiency, the increased availability of Vitamin D products, and recommending that suitable supplements should be available to people with particular dietary needs (for example, people who avoid nuts, are vegan or have a halal or kosher diet). Testing of vitamin D status if someone has symptoms of deficiency or is at very high risk was also recommended.

There is broad acceptance amongst healthcare professionals and Clinical Commissioning Groups (CCGs) of the need to raise awareness of Vitamin D deficiency, not only amongst the healthcare professionals, but also in the UK population, and a general consensus that there is no need to test the vitamin D status routinely in asymptomatic patients. In symptomatic patients, there is a need to measure the vitamin D status if one or more other risk factors are present. The loading dose and maintenance dose of vitamin D can then be prescribed based on the status of the individual. An example of a typical flowchart produced by CCGs to guide non-specialist clinicians through the diagnosis and treatment of vitamin D deficiency is shown in figure 1. This example is taken from the Lancashire Medicines Management Group [Smith, 2013].

Insert Figure 1 here

As most guidelines do not recommend the testing of vitamin D status in asymptomatic adults, SAs remain at high risk of deficiency and potential longer term sequela due to the very high prevalence of vitamin D deficiency in this population, with most individuals remaining asymptomatic. However the most recent SACN report raises the RNI from 0 (1991) to 10 µg/d

for all individuals aged 4 years and above [SACN, 2016]. Current guidelines recommend prevention through advice on regular sunlight exposure, dietary sources of vitamin D and use of "over the counter" vitamin D supplements, giving patient control of vitamin D supplementation. The choice of product should be led by patient preference taking into consideration their beliefs. One specific example is gelatine which is usually derived from pigs and commonly used to encapsulate medications and supplements. In Islam, any products derived from pigs are considered to be unlawful, or "not Halal". Where there is no choice regarding products containing gelatine there is a statement from WHO that permits Muslims to take medicines encapsulated by gelatine, however this still remains a contentious issue amongst Islamic leaders and scholars.

Summary

While there is compelling evidence for an association between vitamin D deficiency and chronic conditions including poor bone health and T2DM, all of which are prevalent in SA ethnic minority groups in the UK, unequivocal evidence of a causal mechanism remains elusive. The most recent reports from SACN and Public Health England recommend that in order to protect musculoskeletal health, serum 25(OH)D should not fall below 25 nmol/l, and that intakes of 10 µg per day are recommended for the UK population over 4 years of age. For SA ethnic minority groups in the UK, meeting these recommendations is likely to require the use of vitamin D supplements year round. New patient care guidelines for non-specialists are required to emphasise this in the primary care setting.

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